Amsterdam I Families without DNA mismatch repair deficiency: Familial Colorectal Cancer Type X

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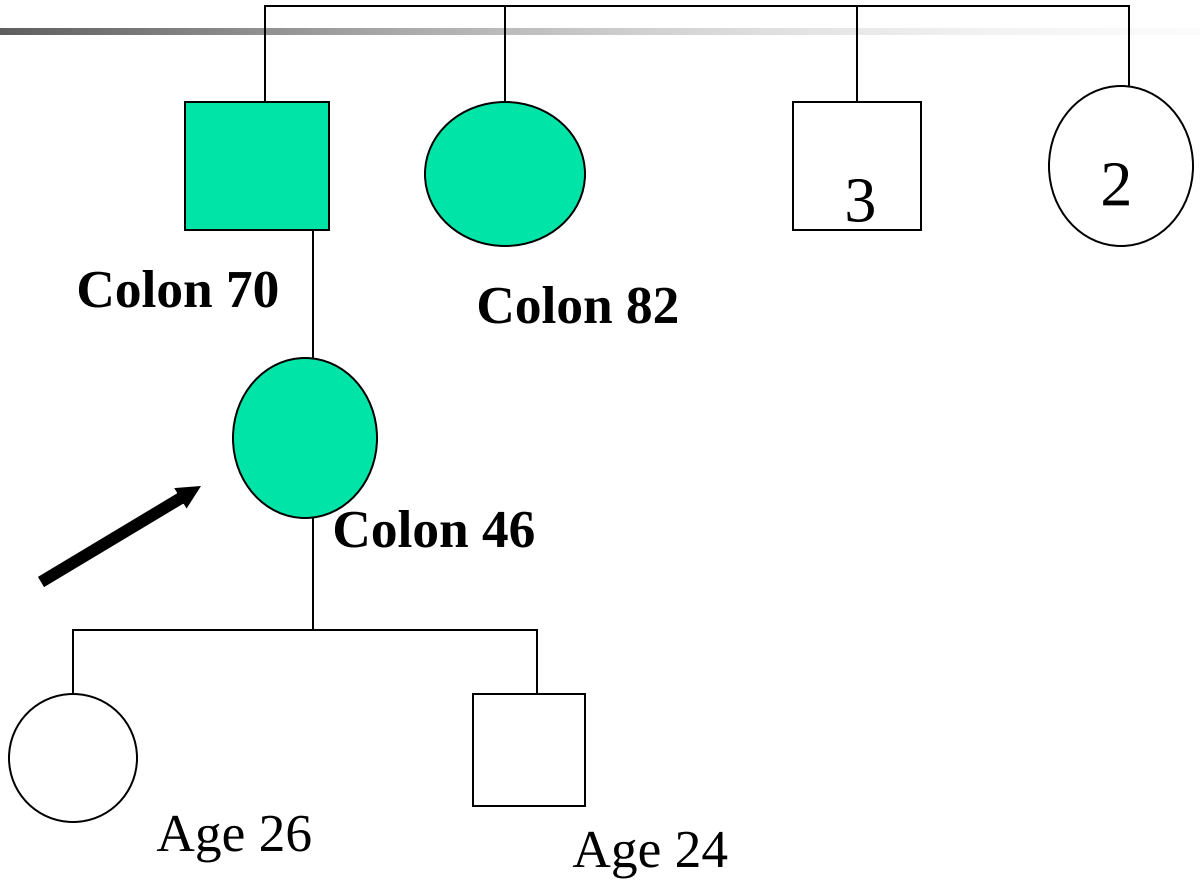
Do I have HNPCC?

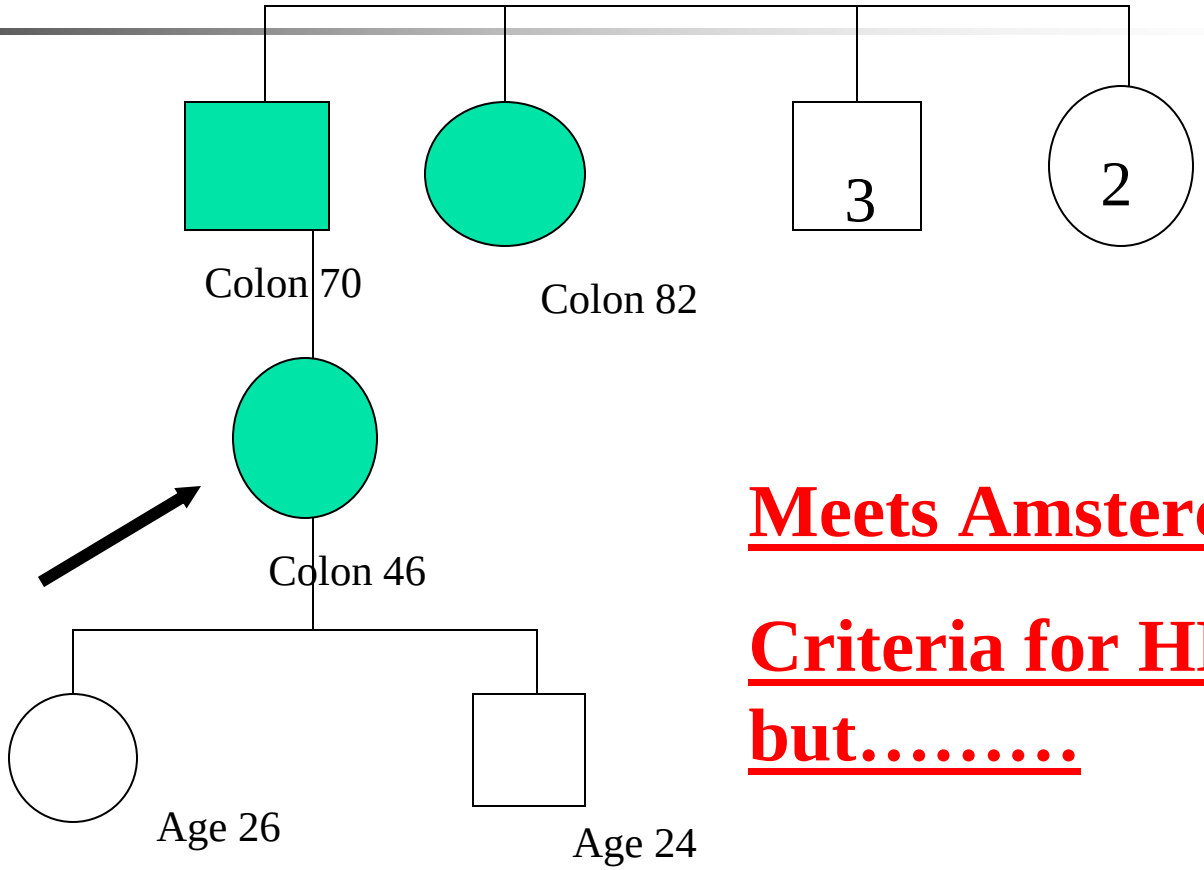


Amsterdam I Criteria

- 3 cases of colorectal cancer;

  two are 1^0 relatives of the third
- One case diagnosed < age 50
- Two generations
- Not FAP

Doctor, do I have HNPCC?



Meets Amsterdam I

Criteria for HNPCC, but……

Assumptions

- **Families that meet Amsterdam criteria most likely to have germline DNA mismatch repair defects (~60%)**
- **If you have HNPCC, you should follow the published screening guidelines--rigorous!!**

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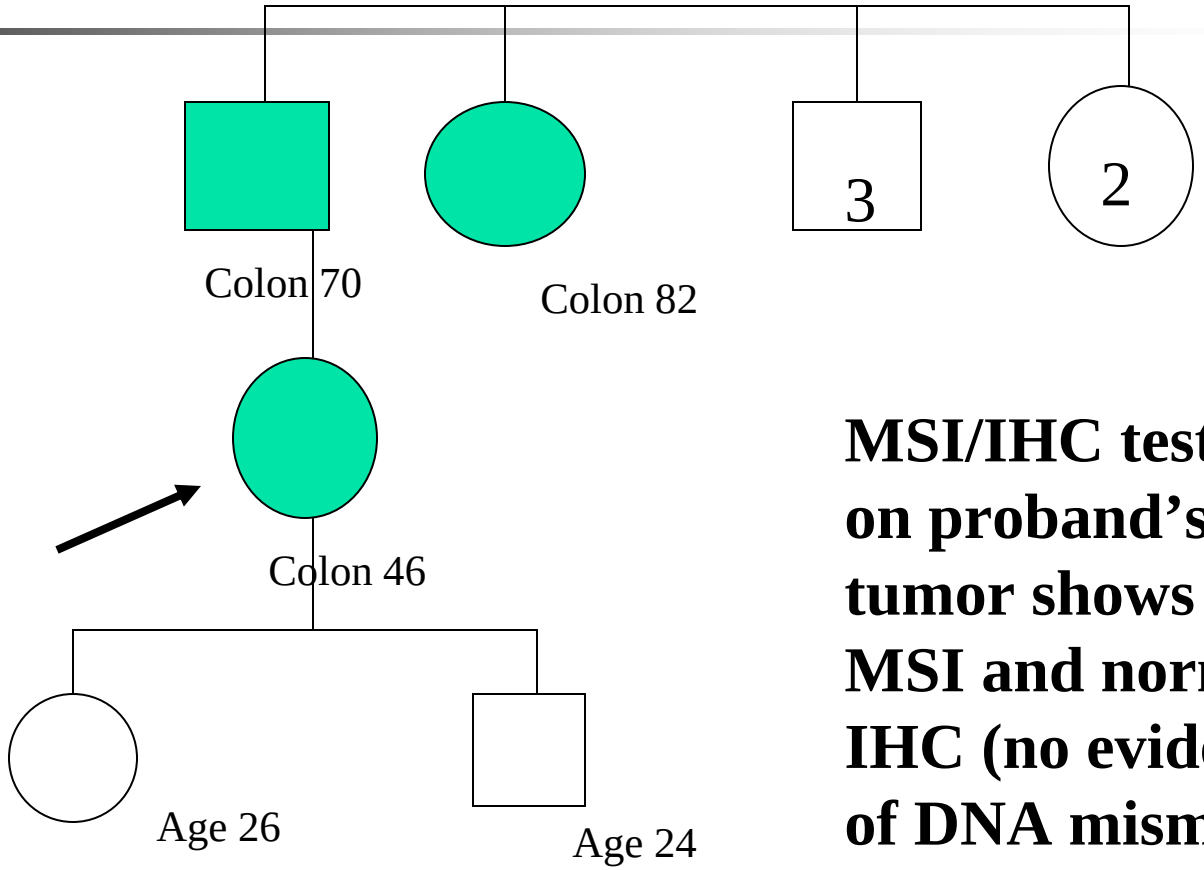


MSI/IHC testing on proband's tumor shows no MSI and normal IHC (no evidence of DNA mismatch repair deficiency)

	AC+	**Not AC+**
DNA MMR defect	AC+/ MMR defect	Not AC+/MMR defect
No DNA MMR defect	**AC+/ no MMR defect**	Not AC+/ no MMR defect

The question

- What are the age related/site specific risks of cancers in families that do fulfill classical Amsterdam I criteria but do not have DNA mismatch repair defects?

The Amsterdam Study

JAMA. 293(16):1979-85, 2005

- 161 families that met Amsterdam I criteria
  - A collaboration of all Colon CFR centers
- Group A = mismatch repair deficiency
  - N=90
    - 51% population-based
- Group B = no mismatch repair deficiency
  - N= 71
    - 65% were population-based
- SIR cancers
  - Pop vs clinic based
  - First vs second degree relatives

Analysis

- Removed “triad” members from the risk analysis
  - Group A→ 1855 relatives
  - Group B→ 1567 relatives

- SIR ratio = observed to expected cases for each 5 yr/sex-specific group, compared to SEER.

Results

- Amsterdam families with MMR gene deficiency showed the expected high cancer risks across multiple cancers
  - Validated our methodology
- **Amsterdam families without MMR gene deficiency showed increased risks for colorectal cancers but no other types of cancers.**
- Even the CRC cancer risk lower in Group B than Group A.

SIR: Group A (MSI-H) vs Group B

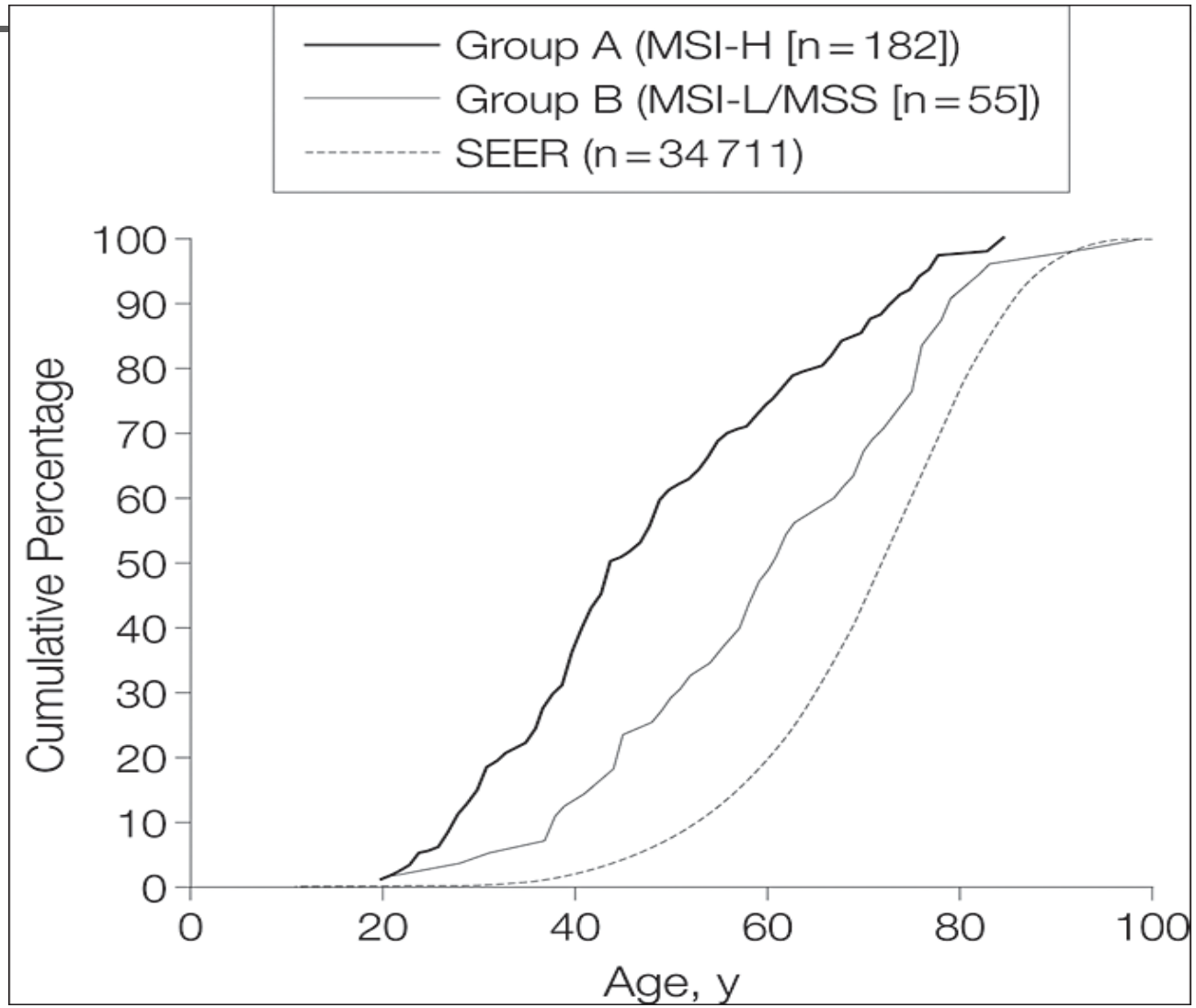
Colorectum:	6.1 vs 2.3	P<0.001
Uterus	4.1 vs 0.8	P <.001
Stomach	4.6 vs 1.4	P=.008
Kidney	2.6 vs 0.9	NS
Ovary	2.0 vs 1.5	NS
Sm intestine	7.6 vs 1.6	NS
Ureter	9.0 vs 2.9	NS

Population cases vs Clinic cases

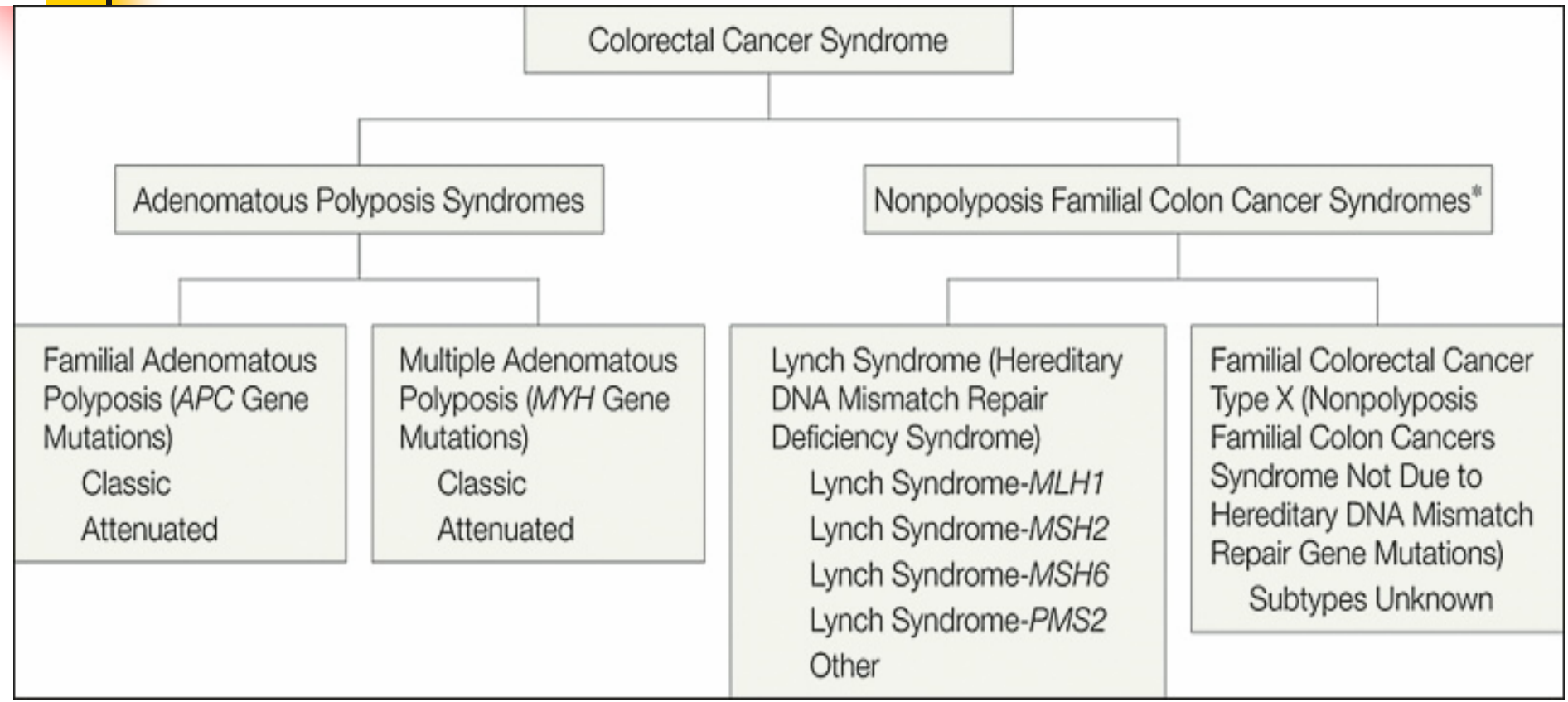
- Clinic-based ascertained cases showed trend toward higher cancer risks than population-based ascertained cases.

- But differences between Groups A (MMR+) and B (MMR-) still significant

Cumulative age onset CRC in non triad relatives (mean 49 years vs 61)



Familial Colorectal Cancer type X



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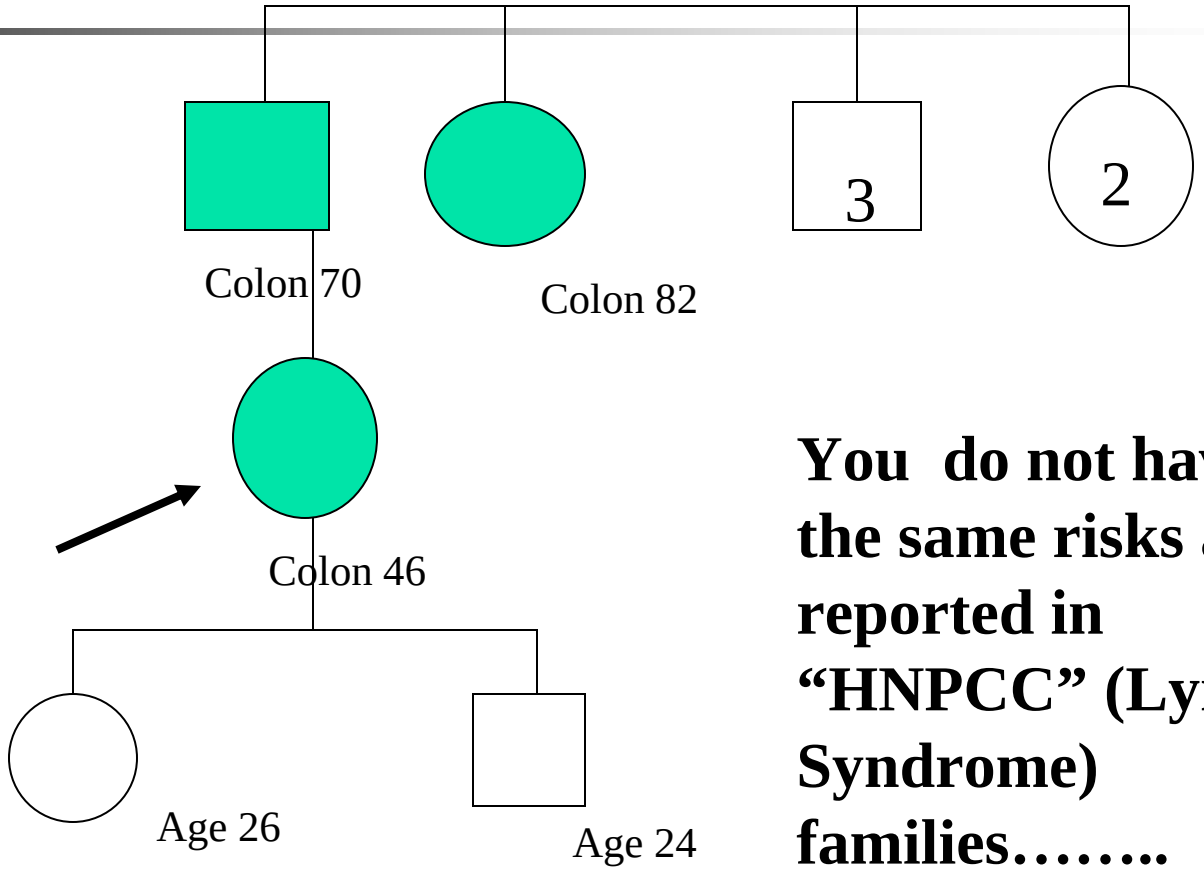

You do not have the same risks as reported in "HNPCC" (Lynch Syndrome) families……..